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Food and Drug Administration
5630 Fishers Lane
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Rockville, MD 20852

Re: Guidance for Industry - BA and BE Studies for Orally Administered Drug Products - General Considerations

I enclose some comments about this draft guidance. I regret that I was unable to submit them earlier and apologize for this.

Yours sincerely,

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Re: Guidance for Industry - BA and BE Studies for Orally Administered Drug Products - General Considerations

I appreciate the opportunity to submit comments about the draft guidance. They will consider mainly issues related to the evaluation of studies of bioavailability (BA) and bioequivalence (BE).

1.A. The general criteria for declaring BE are not stated, except for an implicit indication in the last sentence of Appendix 2. Only exceptions are presented such as for drugs exhibiting nonlinear kinetics and those designated as narrow therapeutic range drugs. Presumably, 90% confidence limits of 80 - 125% are intended for the average BE of AUC and $\epsilon_I = 0.05$ for the individual BE of AUC.

B. Some values for ϵ_I and θ_I are stated but the terms are not defined (but see comment 2 below).

C. Would the regulatory criteria be the same for all metrics, those of total, early and peak exposure? This is not stated, only implied. However, *it would be reasonable to expect **different** criteria for the various metrics* (i.e., different 'goalposts'; Rostami-Hodjegan et al., 1994).

First, C_{max} is known to have larger variation than AUC (see, e.g., Endrenyi and Yan, 1993). This is reasonable since the determination of C_{max} relies on a single observation whereas that of AUC is based on several measurements. This is recognized, for instance, by European regulatory authorities who expect wider bioequivalance limits, typically *70 - 143%, for C_{max},* than for AUC.

Adoption of the same criterion is recommended. As an advantageous consequence, it would not be necessary to reject numerous submissions because they fail the (constant-scaled) criterion of C_{max} but pass it for AUC.

Second, *a measure for early exposure should probably have a different criterion* from that applied to AUC. This was the conclusion of a very recent study of Fossler and Chen (1999) as well as of earlier investigations (Endrenyi and Al-Shaikh, 1995; Macheras et al., 1996; Endrenyi et al., 1998b).

2. It appears to be *premature* to suggest the utilization of the approaches of *population and individual bioequivalence,* to recommend *replicate study designs* for investigations of BE, and to discuss the relevant procedures and criteria (Sections III.A.4, IV, V.C.1, V.D.2). The approaches and their properties are still being studied, and their possible implementation is not expected in the

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near future.

3. The draft guidance recommends that pharmacokinetic measures of *systemic exposure* be used for the assessment of bioequivalence. Notably, indices of early, peak, and total exposure are recommended.

A. The suggestion has an interesting, clinically relevant rationale (Rostami-Hodjegan et al., 1994; Tozer et al., 1996). An alternative view considers that the determination of bioequivalence should aim at pharmaceutical quality control (Endrenyi and Tothfalusi, 1997). This would call for high sensitivity and large statistical power of the contrast.

The difficulty is that either view is not pursued consistently in the draft guidance. It suggests, for instance, that single-dose investigations be generally performed even for modified-release formulations "because a single-dose study is considered more sensitive in assessing the primary question in a BE study "(Section V.D.2: also Section III.A.6).

The same rationale of *sensitivity* is given also when, considering the evaluation of a parent drug and/or metabolites, "determination of only the active moiety and/or active ingredient in the dosage form...is generally recommended" (Section VI.B.l).

B. The alternating views of clinical relevance and pharmaceutical quality control in the draft guidance are confusing and disturbing. A consistent presentation would be clearly preferable.

The ambivalence could be partially resolved if submissions were expected to include measures representing both views. For immediate-release formulations, for instance, the regulatory requirements could be based on metrics of exposure. Nevertheless, measures of quality control would provide additional, relevant, and useful information about the properties and performance of an investigation. Therefore it would be valuable to expect that also these metrics would be reported (as are other measures) together with their characteristics.

4.A. The draft guidance is not consistent in its suggested deviation from 21 CFR 320.1. The draft guidance recommends an emphasis on measurements of *systemic exposure* (Section III.C.8) whereas 21 CFR 320.1 defines BA as the "*rate and extent* to which the active ingredient or active moiety...becomes available at the site of action" (Section II.B). A parallel statutory definition, based on the rate and extent of absorption, is given for bioequivalence (Section II.C).

Even though evaluations of early, peak, and total exposures are proposed, recurring references are made to the rate and extent of absorption (Sections III.A.l, VI.B.3, VI.C). It is stated even in Section III.A.8 where measures of exposure are introduced, that "reliance of systemic measurements should reflect comparable rate and extent of absorption".

The statutory requirement, on the one hand, and the suggestion for utilizing three indices of exposure, on the other hand, are not necessarily contradictory. Only the measure for early exposure is new. Depending on the chosen metric, it measures either the initial or an average rate of absorption.

B. The statement that "direct (e.g., rate constraint and rate profile)...measurements are limited in their ability to assess rate of absorption" (Section III.A.8) is questioned.

A linear rate constant does in fact characterize the initial absorption rate (possibly after some lag time). The rate profile does in fact characterize the time course of absorption rate.

Consequently, it is *possible* to assess the rate of absorption by direct measures (not "measurements"). Procedures have been described in the literature for the evaluation of these measures.

5. It is surprising that "if an early exposure measurement [presumably, 'measure'] is used, *statistical analysis of Cmax is not needed"* both for immediate- and modified- release formulations (Sections V.C.2 and V.D.3). This would be understandable if C_{max} were considered as a metric characterizing the rate of absorption. This unreliable measure would lose its importance if a better early rate metric were also evaluated.

Such considerations, however, would not apply if the metrics were thought to be clinically relevant measures of exposure. C_{max} reflects then the peak response and is generally an important index of safety. Therefore, this measure should be utilized independently and separately from metrics of early exposure.

This is particularly true in assessments of modified-release formulations. Metrics of early exposure do not adequately indicate possible problems of drug safety, including that of dose dumping.

Therefore it could be advisable to *evaluate the bioequivalence of* C_{max} regardless whether a measure of early exposure is or is not determined.

6. The assessment of *different kinds of modified-release formulations* calls for *different approaches.*

A. *Delayed-release formulations* exhibit a lag time for release but otherwise have the kinetic features of immediate-release products. The regulatory expectations for delayed-release products *should parallel those of immediate- and not of modified-release formulations.*

B. *Extended-release formulations* have reduced rates of absorption and can be often described by flip-flop type kinetics. In this case, measurements of early exposure do *not* characterize features of absorption. *Regulatory expectations should involve determinations of AUC and* C_{max}.

C. Truly *modified-release formulations* have strongly altered kinetic features and can not be described by simple models. It could be useful, in this case, to determine measures of early exposure (in addition to AUC and C_{max}). However, there is at present no demonstrated evidence to substantiate this suggestion.

7. The suggestion of *using partial AUC* (Chen, 1992) *as a measure of early exposure is strongly questioned.*

A. Notably, with modified-release formulations, partial AUC measured until either the earlier or the reference peak is expected to exhibit very large variation and small statistical power. The expectation is due to the large uncertainty of the recorded peak time, T_{max}, with these formulations. Other metrics proposed for the evaluation of early concentration-time profiles would have much more favorable properties.

B. Even for immediate-release formulations, the approach suggested in the draft guidance for determining early exposure (Section III.A.8.a) is not favored. As recently reported in joint studies with FDA investigators (Endrenyi et al., 1998 a, b), (1) metrics other than partial AUC are more effective for the purpose, and (2) if partial AUC is used then higher statistical power is achieved with measurements until the earlier of two peaks in each subject.

8. The *scaled criterion* suggested for drugs having *either a narrow therapeutic range or nonlinear kinetics* (Sections V.C.1 and V.D.2) *can be very restrictive and punitive.* (See, however, comment 2 above.)

A. According to the scaled criterion, if the observed (intrasubject) variation of the reference formulation is very small then the equivalent unscaled regulatory limit is very narrow. Consequently, drugs and formulations are strongly penalized if they have favorably small variability and the observations are precise.

The difficulties were recently demonstrated on the assessment of BE for warfarin formulations (Masson and Yacobi, 1999). Using unscaled criteria, both average and individual BE were demonstrated even with tighter limits than those proposed. However, with the scaled criterion, individual BE could not be obtained.

B. The suggested scaled criterion is particularly surprising for drugs exhibiting nonlinear kinetics. The rationale is not clear for suggesting (1) a scaled criterion, and (2) narrow regulatory limits. At any rate, the validity and usefulness of these requirements have not been assessed.

I hope that these comments will usefully assist CDER.

Toronto, December 20, 1999

L. Endrenyi, Ph.D.

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